REMARKS

This Request for Continuing Examination is in reply to the Advisory Action mailed November 27, 2006. Applicants have amended claim 16 as indicated above, and have added new claims 39 and 40. Support for these claim amendments can be found at page 9, lines 1-4 and page 10, lines 1-4, and page 18, 30-lines 9-17, respectively.

Because Applicants respectfully submit that the Patent and Trademark Office has erred in rejecting the unamended claims for the reasons set forth in greater detail below, the amendments made herein were not required as a result of these rejections to render the claims patentable. Rather, the amendments have been made because Applicants wish to present the claims in greater clarity. Therefore, these amendments do not in any way restrict the scope of equivalents otherwise due such claims.

The pending claims are claims 16, 18-22, 30, and 39-40.

Rejection Pursuant to 35 U.S.C. §103(a)

The Advisory Action of November 27th, 2006 (the "Advisory Action") maintains the rejection of pending claims 16, 18-22 and 30 as being allegedly obvious over the primary reference U.S. Patent Application 2002/0040015, to Miller et al., in view first of Granville, (U.S. Patent No. 6,180,402), and further in view of Wheeler et al., EUR. J. OPHTHAL. 9:S17-S21 (Jan-Mar 1999). Applicants respectfully traverse this rejection for the following reasons.

1) *Neither the Miller '015 publication nor the Miller '614 provisional patent application to which it claims priority are prior art to pending claims* 16, 18-22, 30, and 39-40 .

As Applicants have discussed in prior correspondence (e.g., the Replies of December 6, 2005 and March 31, 2006, hereby incorporated by reference herein), the Miller reference is a publication of a non-provisional patent application claiming priority to provisional application No. 60/181,641, filed February 10, 2000. The filing date of the non-provisional patent application was February 9, 2001. The present application has a filing date of October 30, 2001, and claims priority to provisional application 60/244,850, filed November 1, 2000.

Thus, the Patent and Trademark Office must allege that the Miller '015 publication is prior art under 35 U.S.C. §102(e), since the underlying application was both published and filed after the November 1, 2000 priority date of the present application. Under Section 102(e), "a person shall be entitled to a patent unless . . . the invention (in this case, the invention of present claims 16, 18-22, 30, and 39-40) was described in (1) an application for patent, published under section 122(b) [35 U.S.C. 122(b)], by another filed in the United States before the invention by the applicant for patent . . . ." (emphasis added).

Furthermore, a patent application may claim priority to an earlier filed provisional application under 35 USC §119(e), which states that "[a]n application for patent filed under section 111(a) or section 363 of this title [35 USC 111(a) or 363] for an invention disclosed in the manner provided by the first paragraph of section 112 of this title [35 USC 112] in a provisional

application filed under section 111(b) of this title [35 USC 111(b)], by an inventor or inventors named in the provisional application, shall have the same effect, as to such invention, as though filed on the date of the provisional application filed under section 111(b) of this title [35 USC 111(b)]. . . ."(emphasis added).

Section 102(e) is a codification of Justice Holmes' opinion in *Alexander Milburn Co. v. Davis-Bournonville Co.*, 270 U.S. 390 (1926)(hereinafter *Milburn*), in which the United States Supreme Court held that a patent issued to the senior party after (but filed before) the filing date of the junior party's application may constitute prior art against the application, despite not having been used, sold, published or patented before the junior party's filing date because the senior party, having given a "complete and adequate description" of the junior party's invention upon filing his application, "had done all that he could to make his description public. He had taken steps that would make it public as soon as the Patent Office did its work. . . ." *Milburn*, 270 U.S. at 399.

It is clear that in order to serve as a prior art reference under 102(e), the meaning of the term "the invention" in section 102(e)(1), and of "an invention" and "such invention" in section 119(e) must be the same, or in the case of obviousness under 102(e)/103, substantially similar. Otherwise, the rationale behind the *Milburn* decision and the subsequent adoption of section 102(e) makes no sense.

The application of section 102(e)/103 in obviousness questions involving continuation-in-part applications adding new

matter was addressed by Judge Giles Rich, one of the two drafters of the 35 U.S.C. §102(e). Judge Rich, writing for a unanimous 4 judge panel of the Court of Customs and Patent Appeals, first noted that under 35 U.S.C. §102(e) "[a]n abandoned application by itself can never be a [prior art] reference." *In re Wertheim and Mishkin*, 209 USPQ 554, 562 (CCPA 1981)(hereinafter *Wertheim*). Indeed, in situations (like the present one) in which the earlier application's disclosure differs from that of the later patent or publication, *Wertheim* mandates that only if the earlier application (here, the '614 provisional application) provides "a supporting disclosure in compliance with §112" (as required by section 119(e)), of the invention (i.e., the same or similar invention to the one being challenged, as required by 102(e)) is the later reference prior art to the challenged claims. *Wertheim*, 209 USPQ at 564.

In *Wertheim*, the senior party had filed a series of continuations-in-part claiming priority to a great-grandparent application. The USPTO had rejected the junior party's application based upon a disclosure in this great-grandparent application, which was then combined with other, unrelated references to assert a claim of obviousness.

The *Wertheim* court held that the disclosure of the great-grandparent application contained in the later published patent was not prior art to the claims at issue. Judge Rich first held that the USPTO had erroneously abstracted a part of the entire patent disclosure set forth in an application dated earlier than the junior party's filing date, found it "carried over" into the published later patent, and used it in combination with a second reference to reject the junior party's application. *See Wertheim*,

209 USPQ at 562. Judge Rich stated that "such an approach in a situation where there are continuation-in-part applications ignores the rationale behind the Supreme Court decisions in Milburn and Hazeltine [[*Hazeltine Research Inc. v. Brenner*, 382 U.S. 252, 147 USPQ 429 (1965)]that 'but for' the delays in the Patent Office, the patent would have issued earlier and would have been prior art known to the public." *Id.* at 563.

The *Wertheim* court then held that "if a patent could not theoretically have issued the day the application was filed, it is not entitled to be used against another . . . ." *Id.* at 564 (emphasis in original). Therefore, "the determinative question is whether the invention" claimed in the senior party's publication "finds a supporting disclosure in compliance with §112, as required by §120 [and now by section 119(e)]so as to entitle that invention" claimed in the later application the filing date of the earlier application. *Id.* (emphasis in original). "Without such support, the invention, and its accompanying disclosure, cannot be regarding as prior art as of that filing date". *Id.*

Thus, Judge Rich concluded, "only an application disclosing the patentable invention before the addition of new matter, which disclosure is carried over into the patent [or patent publication], can be relied on to give a reference disclosure the benefit of its filing date for the purpose of supporting a 102(e)/103 rejection." *Id.* at 564.

The rationale for the holdings and rules articulated in *Wertheim* remains valid after passage of the American Inventors Protection Act of November 29, 2000, which amended 35 U.S.C. 102(e) to pertain to published U.S. patent applications as well as

granted patents. Although *Wertheim* discussed granted patents, the justification for the section 102(e) rule remains the same: the senior part who has done everything in his power to disclose "the invention" should not be penalized for patent office delay.

Conversely, as held by *Wertheim*, if an earlier provisional or non-provisional application does not disclose the invention claimed in the published patent application in conformity with section 112, 1st paragraph, then the entire purpose of the *Milburn* rule (and therefore section 102(e)) is subverted. Certainly the published patent application is available as prior art as of its publication date if it meets the requirements of 35 U.S.C. §§ 102(a) & (b); however, if the earlier application did not contain sufficient section 112 support for the invention claimed in the published patent application, *Wertheim* mandates that it cannot be considered as prior art as of the filing date of the earlier application.

Additionally, the rationale of *Wertheim* carries through even when the asserted prior art is a patent publication rather than a patent. Section 119(e) provides that a non-provisional application filed "for an invention disclosed [by at least one common inventor in a properly filed earlier provisional application] in the manner provided by the first paragraph of section 112 . . . shall have the same effect, as to such invention, as though filed on the date of the provisional application. . . ."

Thus, clearly, the ability of a later application to claim priority to an earlier provisional application only applies with regard to the invention disclosed in the provisional application

which fully conforms with the enablement, written description, and best mode requirements of section 112.

In the present case, the Advisory Action attempts to utilize the Miller reference as 102(e)/103 prior art against present claims 16, 18-22, 30, and 39-40. In brief, these claims are drawn to a method of protecting ocular neural tissue of a patient's eye from damage caused by a photodynamic therapy (PDT) treatment, the method comprising the steps of administering a PDT treatment to the eye of the patient, and delivering a composition to said patient's ocular neural tissue, wherein the composition comprises an effective amount of brimonidine, a neuroprotectant.

The Miller '015 publication contains claims drawn to a method of treating unwanted choroidal neovascularization by administering PDT and an apoptosis-modulating factor (see claims 20-31). However, this publication has a filing date after the priority date of the present application.

The Miller '614 provisional application does not contain any disclosure of using PDT in conjunction with an apoptosis-modulating factor, much less a disclosure meeting the enablement, written description, and best mode requirements of section 112, 1st paragraph, as required by both section 119(e) and *Wertheim*.

Therefore under *Wertheim* the Office cannot simply utilize any portion of the '015 Miller reference as "prior art", even with respect to portions present in the original '614 provisional application. For the reasons stated above, Applicants submit that the Miller '015 publication is not prior art to the presently pending claims.

The combination of the remaining references, Granville and Wheeler, do not render pending claims 16, 18-22, 30, and 39-application obvious. As stated in the March 31, 2006 and September 27, 2006 Replies, hereby incorporated by reference, Granville does not disclose brimonidine, neuroprotection, or ocvular neurtal cells, much less discuss administering a neuroprotectant or anti-apoptosis agent to ocular neural cells. Granville is largely concerned with the treatment of tumors and other cancers, and is concerned with PDT-caused damage to the immune system of the subject. Granville does disclose using compounds effective to prevent apoptosis *in vitro* in cultured cells of blood lineage (and discusses the prevention of T-cell death), but this reference does not discuss the use of PDT in combination with apoptosis-modulating agents in the eye, and makes it very clear that apoptosis inhibitors in certain cell lines may be apoptosis promoters in other cell lines, Granville, column 3, lines 4-9, thus clearly warning that each candidate compound to be used as a apoptosis-modulating factor must be carefully tested to ensure that it will not kill surrounding cells. There is no intimation that this technique may be helpful in the treatment of neural tissue.

Wheeler discusses glaucoma, and discloses that brimonidine is a neuroprotectant, that it protects retinal ganglion cells in models of retinal injury. These models have nothing to do with PDT. The first model is mechanical injury (crush with a calibrated force) to the optic nerve. The second model involves inducing ischemia by raising intraocular pressure in rats to 110 mm Hg for 50 minutes, followed by reperfusion; this is also at least partly a mechanical injury, as the increased intraocular

pressure leads to the crushes the intraocular retinal ganglion cells.

The Examiner characterizes Wheeler as having disclosed "an antipoptotic neuroprotectant which increases bcl-2 expression." Advisory Action, page 2, paragraph 5 and 6; page 3, last paragraph. Applicants respectfully disagree and submit that this statement is an illustration clear example of the insidious nature of hindsight.

Wheeler does not disclose that brimonidine is anti-apoptotic or that it increases bcl-2 expression. Indeed, Wheeler makes clear that the damage caused by glaucomatous optic neuropathy is only "likely" to be through programmed cell death. Wheeler, last paragraph. Wheeler states that brimonidine conferred neuroprotection in the two indicated models of glaucomatous optic neuropathy. Wheeler then makes clear that "the mechanism of neuroprotection has not been fully elucidated", and that it "may involve the induction of anti-apoptotic genes such as bcl-2" *Id.* (emphasis added).

Wheeler concludes with the following sentence: "[u]nravelling the mechanism by which treatment with $\alpha 2$ agonists such as brimonidine confers neuroprotection to retinal ganglion cells may reveal new therapeutic intervention points in glaucoma or other optic neuropathies." *Id.*

Thus, far from "disclosing" that brimonidine is anti-apoptotic and induces bcl-2 expression, Wheeler makes clear that it was at that time not known if bcl-2 is involved in damage to retinal ganglion cells, nor was it known by what mechanism

neuroprotection is conferred by brimonidine. Indeed, Wheeler's last sentence is as clear an "invitation to experiment" in order to learn the answer to these questions as can be imagined. Only through the lens of hindsight could this statement lead to the conclusion that Wheeler discloses that brimonidine is anti-apopotic and increases bcl-2 expression. And although it is true that one must examine a patent claim with some prior knowledge ("inevitable" hindsight) concerning what is claimed, Applicants believe that the hindsight employed by the PTO in this instance is clearly based on knowledge of at least the present specification and the portions of the Miller publication having an effective filing date after the filing date of the present specification (such as claims 20-31 and their supporting disclosure).

The person of ordinary skill in the art having knowledge of Granville and Wheeler would have no reason to combine the references to make the present invention. Neither reference discusses PDT in the eye. Neither reference suggests any reason why one would want to combine brimonidine with PDT to prevent damage to ocular neural tissue, or even assuming arguendo that such suggestion did exist, any reasonable expectation that brimonidine would function in the eye to protect neurons from PDT as the anti-apoptotic agents of Granville seem to do *in vitro* to protect cultured cells of the blood lineage.

At best (and without making any admission whatsoever), the combination of Granville and Wheeler might lead a person of ordinary skill in the art to do as Wheeler suggests and attempt to unravel the mechanism by which treatment with $\alpha 2$ agonists such as brimonidine confers neuroprotection to retinal ganglion cells. However, this is merely an invitation to experiment - and asn

invitation to experiment will not support a finding of obviousness under 35 U.S.C. § 103.

2) *Even if the Miller '015 reference were prior art to pending claims* 16, 18-22, 30, and 39-40, these claims are not prima facie obvious, since Miller adds nothing to the combination of Granville and Wheeler concerning the use of brimonidine in conjunction with PDT.

Even if the Miller '015 publication were prior art to the presently pending claims, its combination with Granville and Wheeler would not render the present claims prima facie obvious.

The Miller '015 publication is based on a non-provisional patent application and claims 20-31 and their supporting disclosure, dealing with PDT in conjunction with anti-apoptosis factors, have an effective filing date of February 9, 2001, after the filed November 1, 2000 effective filing date of the present application, and thus this subject matter is not prior art to the presently pending claims.

Nevertheless, the Patent and Trademark Office has stated that Miller is relevant because 1) it allegedly demonstrates that PDT was used in conjunction with anti-angiogenic factors to increase the efficacy and selectivity of PDT, and 2) it teaches that the antiangiogenic factor potentiates the cytotoxicity of the PDT; while "[i]n addition, the anti-angiogenesis factor can enhance the specificity of photodynamic therapy, for example, by permitting occlusion of the choroidal neovasculature while at the same [time] sparing the surrounding blood vessels, for example, normal choroidal vasculature, and/or surrounding tissue, for example, the overlying neurosensory retina." This sentence appears on page 3 of the '614 provisional application. The Patent and Trademark

Office concludes that this phrase "not only suggests, but actually teaches that neuroprotection is desired." Advisory Action, page 2, 4th paragraph.

Again, and respectfully, Applicants must emphasize this is not what the quoted phrase suggests or teaches, and that the PTO's conclusion that it does can only be the result of hindsight in view of the present specification and the prohibited portion of the '015 reference.

To see why this is true it is important to consider the morphology of the retina. The "neurosensory retina" consists of various layers of cells, not all of them neurons. Beginning with the innermost layer, there is the inner limiting membrane, followed by a layer comprising the retinal ganglion cells, the amacrine cells, the bipolar cells, the horizontal cells, the photoreceptors, and an outer layer comprising the retinal pigment epithelium (RPE). Applicants are hereby providing a diagram of the retina available on the University of Utah website for the Examiner's convenience. Neither the inner limiting membrane nor the outer RPE cell layers comprise neurons. So "sparing the neurosensory retina" in the Miller '614 provisional application does not necessarily refer to protecting neural cells; it may mean protecting the inner or outer non-neural layers.

Therefore, to determine the meaning of the term "neurosensory retina" used by Miller in the phrase quoted by the Office, it is necessary to look to the remainder of this reference, which, of course, must be considered as a whole.

First, Applicants note the '614 provisional makes no specific reference to protecting or "sparing" neurons.

Secondly, the '614 provisional consistently does specifically refer to protecting the RPE (epithelial cell) layer of the retina; thus on page 11, second full paragraph, the provisional application discusses the fact that 1) PDT is toxic to the RPE, and that it may be possible to prime the target cells to be more susceptible to PDT while "thereby decreas[ing] the effect on surrounding cells such as RPE." This suggests not neuroprotection, but protection of epitheial cells. Similar disclosure can be found at page 15, 2nd full paragraph, Examples 3, and 4, page 23, Example 3 ("toxicity towards RPE also proceeds by programmed cell death", page 24, lines 1 and 2, page 26 ("angiostatin specifically targets retinal endothelial cells and induces apoptosis, without apparent effect on the RPE.")

Finally, almost the exact language cited by the Office is again used on page 8 of the specification, as follows: "In addition, the anti-angiogenesis factor can enhance the specificity of PDT, for example, by permitting occlusion of the choroidal neovascularization while at the same [time] sparing the surrounding blood vessels, for example, normal choroidal vasculature, and/or surrounding tissue, for example, the retinal epithelium." (emphasis added).

Therefore, the only reasonable conclusion is that the meaning of "neurosensory retina" in the passage cited by the Examiner must refer to the RPE portion of the retina, rather than the neurons themselves. This would be the understanding of the person of

ordinary skill in the art reading this reference as of the filing date of the present application.

Thus, the '614 provisional application does not suggest or teach neuroprotection, but rather protection of the RPE.

Moreover, as has been stated in prior Replies, this reference teaches away from the present invention by expressly teaching combining PDT with the ocular administration of apoptosis promoting agents. As stated above, Applicants hereby incorporate by reference the arguments made in prior Replies.

In response the Office argues that because 1) Miller is silent about the use of anti-apoptotic agents as a neuroprotectant, 2) Miller's use of pro-apoptotic agents with PDT is for a different purpose than neuroprotection (enhancement of cytotoxicity in the target neovasculature, Miller does not teach away from the present invention.

First, Applicants respectfully refer to the disclosure of page 11 of the Miller '614 provisional in which the object of "priming" vascular endothelial cells with an pro-apoptotic agent is to "thereby decrease the effect on the RPE", a non target retinal tissue. Thus, the Office's conclusion, that Miller does not teach away because it teaches enhancing cytotoxicity of target tissue, while brimonidine is used in the present invention as an agent to protect the non-target tissue, is not credible and again can only be attributed to a hindsight reconstruction of the present invention.

Miller's combination with Granville and Wheeler still provides no incentive for the person of ordinary skill in the art to make the present invention, comprising the steps of conducting PDT on the eye of an individual and administering brimonidine to the ocular neural tissue of such individual to present PDT damage caused by the PDT. As the Office indicates in the Advisory Action, the portions of Miller is silent about the use of anti-apoptotic agents as a neuroprotectant. Far from filling this gap, Granville is also silent about neuroprotection, and Wheeler makes clear that it was at that time not known by what mechanism neuroprotection is conferred by brimonidine.

Moreover, as stated above, there is simply no indication in the combined references why one of skill in the art would specifically seek to carry out the steps of the present method at the priority date of the present application. Even if one were to assume that the combined references convey the motivation for using an anti-apoptosis agent in conjunction with PDT with a reasonable expectation of success, brimonidine was not known to be such an agent at the time the presently claimed invention was originally disclosed by the Applicants.

For these reasons the Applicants respectfully request reconsideration and withdrawal of the present rejections.

CONCLUSION

For the reasons given above, the claims are now thought to be in condition for allowance, and a Notice to that effect is earnestly sought.

This Request for Continued Prosecution is being made along with a request for a six-month extension of time. Kindly use Deposit Account 01-0885 for the payment of any such fee now due, or to credit any overpayment.

Respectfully submitted,

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